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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,644	01/15/2004	Peter Wernet	07588/026003	5815

21559 7590 10/28/2005

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,644	WERNET, PETER	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3,5-9,12-15 and 17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,10,11 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 are pending in the present application.

Applicant's election without traverse of Group II (Claims 1-2, 4, 10-11 and 16) in the reply filed on 10/11/05 is acknowledged.

Accordingly, claims 3, 5-9, 12-15 and 17-21 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 1-2, 4, 10-11 and 16, drawn to a method for treating a disease of the cardiac muscle in a human patient comprising administering to the patient unrestricted somatic stem cells (Invention of Group II, see Office action mailed on 9/6/05), are examined on the merits herein.

Claim Objections

Claims 10-11 and 16 are objected to because they recite a non-elected embodiment, specifically "differentiated progeny of USSCs". Appropriate correction is required. Please note that claims 10-11 and 16 **do not link** the various distinct treatment methods using USSCs with the various distinct treatment methods using differentiated progeny of USSCs.

Claims 4 and 16 are objected to because they recite a non-elected embodiment, specifically "smooth muscle". Appropriate correction is required.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4, 10-11 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of treating any disease other than diseases of the connective tissue, bone or cartilage, with a disease of a cardiac muscle as the elected invention, in a human patient, said method comprises administering to said patient any unrestricted somatic stem cells (USSC).

Apart from disclosing the isolation of a population of adherent, fibroblastoid-shaped cells (USSC cells) obtained after culturing mononuclear cells isolated from human umbilical cord blood, and **wherein the adherent, fibroblastoid-shaped cells are CD34$^-$, CD45$^-$, CD14$^-$, CD13+, CD29+ and CD49e+**, and that these cells are capable to differentiate *in vitro* into CD34+ hematopoietic progenitors or/and Flk1+

progenitors, mesenchymal progenitors with osteogenic, chondrogenic, adipogenic differentiation potentials as well as neural stem cells under suitable culture conditions, the instant speciation fails to provide any description for any other so-called "unrestricted somatic stem cells" populations derived from any tissue and/or animal sources to be utilized in the treatment methods as claimed. What are the essential characteristics or elements possessed by other populations of unrestricted somatic stem cells other than the cell population of adherent, fibroblastoid-shaped cells that have the immunophenotype of $CD34^-$, $CD45^-$, $CD14^-$, CD13+, CD29+ and CD49e+? Therefore, the instant disclosure does not reasonably convey to a skilled artisan at the time the invention was made that Applicant was in possession of a broad genus of "unrestricted somatic stem cells" to administer into a human patient for treating any disease other than the diseases of the connective tissue, bone or cartilage.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot fully envision the detailed structure of a broad genus of "unrestricted somatic stem cells" apart from the single disclosed cell population of **adherent, fibroblastoid-shaped cells that are $CD34^-$, $CD45^-$, $CD14^-$, CD13+, CD29+ and CD49e+**, to be utilized in the treatment

method as claimed, and therefore conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or characterizing it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-2, 4, 10-11 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the instant specification is not enabled for the following reasons.

(a) The breadth of the claims

The instant claims encompass a method of treating any disease other than diseases of the connective tissue, bone or cartilage, particularly with any disease of a cardiac muscle as the elected invention, in a human patient, said method comprises administering to said patient any unrestricted somatic stem cells (USSC) derived from any source (autologous, allogeneic and xenogeneic sources).

(b) The state and the unpredictability of the art

At the effective filing date of the present application (11/3/00), little was known on the existence of an "unrestricted somatic stem cell" population that is capable to differentiate into mesenchymal stem cells, haematopoietic lineage stem cells, neural stem cells and endothelial stem cells in the prior art. There is also a significant skepticism or doubt on the plasticity of adult stem cells reported in the literature at about the effective filing date of the present application (Vogel, Science 295:1989-1991, 2002; IDS; Holden et al., Science 296:2126-2129, 20002; IDS; Verfaillie et al., Hematology 369-391, 2002; IDS). Verfaillie et al. state "If studies indicating that adult stem cells may have greater differentiation potential can be confirmed and extended, adult stem cells, like their embryonic counterparts, may be used to treat degenerative or genetic disorders of many more organs. However, studies to convincingly prove this thesis will be required. In addition, a large amount of work lays ahead to determine how such cells would be used." (page 386, col. 2, top of second paragraph); "Whether multi- or

pluripotent adult stem cells will have the same longevity and *in vivo* functional differentiation potential as ES cells still needs to be proven in studies in which both cell sources are compared side by side" (page 387, col. 1, bottom of first paragraph). Furthermore, the art on the use of any stem cell population for the treatment of a liver disease, a vascular disease, a disease of a nervous tissue or for this instance the disease of the cardiac muscle was and continues to be nascent and unpredictable as evidenced at least by the teachings of Andrea-Romana et al. (Human Reprod. 18:1489-1493, 2003); Park et al. (Gene Therapy 9:613-624, 2002); Kaufman et al. (PNAS 98:10716-10721, 2001) and Grounds et al. (J. Histochem. Cytochem. 50:589-610, 2002).

In 2003, Andrea-Romana et al. still state "It is **the hope** of investigators and patients alike that in future the isolation of pluripotent human stem cells **will allow the establishment of therapeutic concepts** for a wide variety of diseases" (see abstract), and "We believe the findings reported here, ..., to be encouraging for **the further investigation** of human amniotic fluid as a putative new source of stem cells with high potency" (page 1492, col. 2, last paragraph). With respect to the issue on global gene and cell replacement strategies via stem cells, Park et al. state "**The field of NSC biology is at a very early stage of development. Many of our suggestions are highly speculative**, and much needs to be learned about the properties of such cells. While work is ongoing on the isolation, propagation, and transplantation of hNSCs, **many important questions need to be addressed experimentally before using such cells in clinical applications**. For instance, what factors optimize the expansion,

stability, engraftment, migration and differentiation of transplanted NSCs? **What variables dictate the efficiency of foreign gene expression by engrafted NSCs**?....When is the proper time to administer cells? What are the limits of reconstitution in the brain? Do donor-derived cells function normally?" (page 622, column 2, last paragraph continues to line 2 of column 1 on page 623). Kaufman et al. state "**If** human ES cell-derived HSCs can be used to create hematopoietic chimerism in a patient, that patient should be tolerant to other tissues derived from the same ES cells and would not require any continuous immunosuppressive treatment", and "The clinical promise of human ES cell-base therapies is great; however, because these therapies will be entirely novel, serious concerns about safety and efficacy will need to be addressed before human clinical trials can be initiated" (page 10721, col. 1). Grounds et al. teach that although it has been shown in tissue culture that human ES cells can also differentiate into cardiomyocytes, human ES cells have a very low efficiency of conversion into cardiomyocytes compared with those of mice (<10% compared with >80% of murine ES cells; a median of 11 days for differentiation compared with 2 days for murine cells), and that the use of embryonic stem cells as a source of cardiomyocytes is an attractive therapeutic possibility that needs to be fully explored (page 604, col. 2 under the section titled "Embryonic stem cells").

(c) The amount of direction or guidance presented

Apart from the disclosure of a population of adherent, fibroblastoid-shaped cells (USSC cells) having an immunophenotype of **$CD34^-$, $CD45^-$, $CD14^-$, CD13+, CD29+ and CD49e+**, obtained after culturing mononuclear cells isolated from human umbilical

cord blood, and wherein these cells are capable to differentiate into CD34+ hematopoietic progenitors or/and Flk1+ progenitors, mesenchymal progenitors with osteogenic, chondrogenic, adipogenic differentiation potentials and neural stem cells under suitable culture conditions, the instant specification fails to provide sufficient guidance for a skilled artisan on how to obtain any other cell populations that has the same unrestricted pluripotent differentiation potential to be utilized a method of treating any disease other than diseases of the connective tissue, bone or cartilage in a human patient, including the any disease of the cardiac muscle.

Even with the disclosed cell population having the immunophenotype of **CD34$^-$, CD45$^-$, CD14$^-$, CD13+, CD29+ and CD49e+**, there is no evidence of record indicating or even suggesting that this cell population is capable of targeting to the desired tissue site (e.g., the diseased cardiac tissue) from any administering site in a human patient, engrafting, proliferating and differentiating into any resident cells of the targeted tissue in a sufficient number to yield any therapeutic effects for the treatment method as claimed. It is unclear that the differentiated cells in the targeted tissue from the so-called "unrestricted somatic stem cells" of the present invention are even functional *in vivo* and that they function in a compatible manner with existing resident cells to yield any therapeutic effect contemplated by Applicants. Particularly, on the basis of the application as filed, there is no indication whatever that the "unrestricted somatic stem cell" population of the present invention is capable of differentiating into any cardiomyocyte *in vitro*, let alone for the *in vivo* situation. Furthermore, would any "unrestricted somatic stem cells" population derived from any source, particularly from a

xenogenic source withstand against an adverse host immune response and still yield the desired therapeutic effects?

Once again, with the lack of sufficient guidance provided by the present application, and in light of the state of the art at the effective filing date of the present application, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

(d) Working example provided

There is an absence of an example demonstrating that any therapeutic effect has been attained or achieved in any human patient for any disease other than diseases of the connective tissue, bone or cartilage, particularly the disease of the cardiac muscle, using any "unrestricted somatic stem cells" population.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art and particularly for obtaining any therapeutic effects using any "unrestricted somatic stem cells" population for treating any disease of the cardiac muscle in a human patient (the elected invention), and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4, 10-11 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 10 and their dependent claims, it is unclear what is encompassed by the phrase "other than diseases of the connective tissue, bone, or cartilage". Which connective tissue does Applicant refer to? Additionally, in claims 4 and 16, the phrase "said disease is a disease of the cardiac muscle or smooth muscle" appears to be contradictory to the preamble "other than diseases of the connective tissue" recited in independent claims 1 and 10 because muscle is considered to be a connective tissue as evidenced by the teachings of Bruder et al. (WO 97/39104; page 4, lines 1-2; claim 15). Clarification is requested because the metes and bounds of the claims are not clearly determined.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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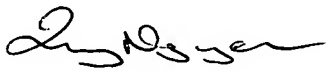

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PATENT EXAMINER